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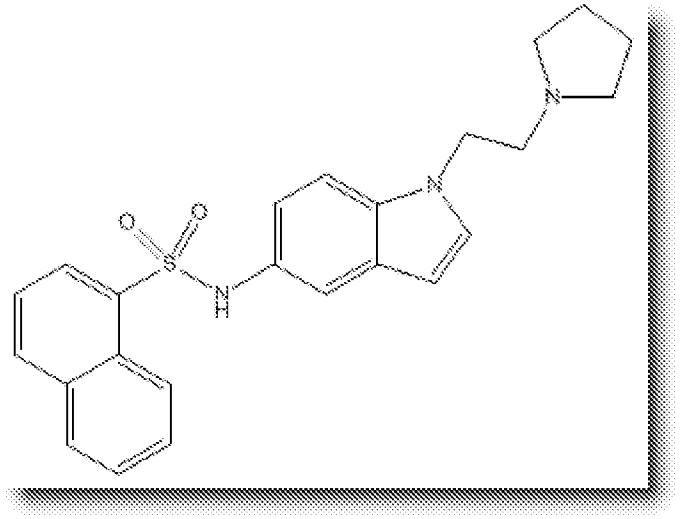
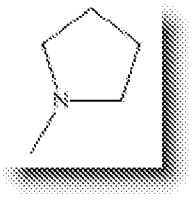
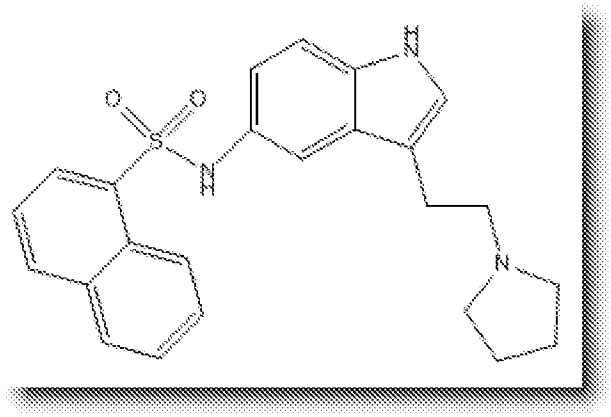
11. The request for reconsideration has been considered but does NOT place the application in condition for allowance because:

1. As discussed in the previous Action mailed on 02/23/200+, the instant invention is drawn to compounds which are useful as 5-HT_6 modulators. Specifically, instant claim 1 is drawn to compounds of formula (Ia) which encompasses the following specific compound



wherein R1 is NR^8R^9 and R^8R^9 together with the bridging nitrogen atom form a saturated heterocyclic ring, specifically  ; R2-R7 are hydrogen; and A is a polycyclic aromatic ring system, wherein the rings are 6 membered. Specifically, the above compound is disclosed in the instant Specification as N-[1-(2-pyrrolidine-1-yl-ethyl)-1H-indole-5-yl]-naphthalene-1-sulfonamide (Page 78, Example 17) and the compound reads on claims 1-8 and 76-82.

2. *Merce-Vidal et al* teach compounds which are useful as 5-HT_6 modulators. In particular, *Merce-Vidal et al* disclose the compound N-{3-[2-(pyrrolidin-1-yl)-ethyl]-1H-indole-5-yl}-naphthalene-1-sulfonamide, having the following structure:



(Page 6, Example 45). Accordingly, the **only** difference between the instant species and that taught by *Merce-Vidal et al* is the placement of -$(CH_2)_n$-R_1 (wherein -$(CH_2)_n$-R_1 in the instant invention and in *Merce-Vidal et al* are the same) on the indole core. As discussed in the previous Action, the compounds are thus positional isomers of each other, and the subtle difference between the compound taught by *Merce-Vidal et al* and the instantly claimed species is *prima facie* obvious in view of *In re Wilder*, 563 F.2d 457 (CCPA 1977).

3. Applicants, however, traverse this finding on the grounds that *In re Wilder* notes that such positional isomers are ***generally*** of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties and, in the instant case, "even if it were the case that the claimed compounds are simply position isomers or homologs of the compounds disclosed by *Merce-Vidal et al*, Applicants… have provided bibliographic evidences... to provide that the different biological properties between 1-substituted and 3-substituted indoles are known from the prior art" (Applicant Argument, Page 7). Indeed, as

noted by the court in *Takeda Chemical Industries, LTD. V. Alphapharm PTY., LTD.*, 492 F.3d 1350, citing *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995), "'[n]ormally a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound.' That is so because close or established '[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds.' A known compound may suggest its homolog, analog, or isomer because such compounds 'often have similar properties and therefor chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.'" (at page 1356). However, the court (quoting *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985) also noted that "since our *Wilder* decision, we have cautioned 'that generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious from one another'" (at page 1361) and that "in order to find a *prima facie* case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required." (at page 1356). Thus, in *Takeda*, the court found no motivation existed in the prior art for one of ordinary skill in the art to modify a prior art compound by homologation **and** ring-walking to arrive at the claimed compound **and** wherein the claimed compound further exhibited unexpectedly superior properties over the prior art compound.

4. Despite Applicants assertions, the instant case is distinguishable from *Takeda* in that the prior art compound taught by *Merce-Vidal et al* differs from the instantly claimed compound in only **one** respect (i.e., ring walking the moiety from position 3 to position 1) whereas in *Takeda*, the compounds differed in **two** respects. Furthermore, no where have Applicants provided

evidence to suggest that the one difference in the instant case, i.e., the ring walking, was **not** a routine step in the drug optimization process at the time the instant invention was made (as was the case in *Takeda*; see page 1360). Also, unlike in *Takeda*, the specific molecular modifications necessary to achieve the claimed invention are motivated in further view of *Filla et al*. As previously discussed, *Filla et al* teach compounds which (like *Merce-Vidal et al*) are 5-HT_6 modulators possessing an indole core. However, the compounds of *Filla et al* are substituted at position 1 of the indole core. Accordingly, the skilled artisan - who would ordinarily contemplate making isomers of the compound taught by *Merce-Vidal et al* to try to obtain compounds with improved properties - would consider ring-walking the moiety to position 1 of the indole core with the reasonable expectation that compounds possessing such modification would still function as 5-HT_6 modulators and possibly possess improved properties. Finally, there is nothing in the record to indicate that the instantly claimed compound possesses any unexpectedly superior properties over the prior art compound taught by *Merce-Vidal et al* such as, for example, reduced toxicity (as in *Takeda*) to overcome this *prima facie* rejection.

5. Applicants point to indole-containing compounds which are positional isomers of each other but which have distinct activities (Applicant Argument, Pages 8-9). However, Applicants' argument remains unpersuasive since, as previously noted, none of the compounds referenced are drawn to modulators of 5-HT6. Furthermore, although it is clear that the referenced compounds are known to have different activities, it is not clear that the compounds also ***lack*** the same activity. That is, whereas compound (1) is claimed as an inhibitor of thromboxane A2 synthesis in WO 9320065 while it's positional isomer compound (2) is described as a selective h5-HT1D receptor agonist, there is no evidence that compound (1) was assayed to evaluate its

activity as a selective h5-HT1D receptor agonist and was determined to not possess such activity, and *vice versa*. The same reasoning applies to the compounds relied on by Applicants at Pages 9-10; namely, there is nothing to suggest that the RN 137642-51-4 does not possess 5-HT_6 activity even though it is not indicated as such. Moreover, *assuming arguendo* that RN 137642-51-4 does not possess such 5-HT_6 activity, since the compounds differ in three respects (two ring walking modifications and one halogen substution) it would be impossible to ascertain whether the difference in activity was due to a single ring-walking modification as in the instant case. Additionally, the fact that the instant compound does not possess a tryptamine-like structure is not considered persuasive. Example 28 in *Filla et al* (Page 67) does not appear to possess a tryptamine-like structure any more than the instantly claimed compound possesses said structure, yet Example 28 is disclosed as a 5-HT6 modulator. Thus, it is not found persuasive that the skilled artisan would have expected maintaining the tryptamine-like structure in the compounds taught by *Merce-Vidal et al* to be critcal for their activity as 5-HT6 modulators.

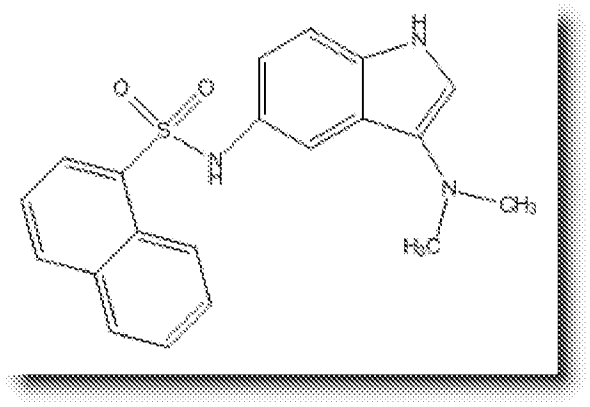
6. Thus, since Applicants have not provided evidence to demonstrate that ring walking was not a routine step in the drug optimization process at the time the instant invention was made and since Applicants have also not introduced sufficient evidence to overcome the presumption that positional isomers are ***generally*** of sufficiently close structural similarity that such compounds possess similar properties, the arguments are not found persuasive.

7. Applicants further argue that *Filla et al* (which discloses 5-HT_6 receptor modulators possessing an indole core which is substituted at position 1) does not contain the exact substituent at position 1 as is disclosed by the prior art compound taught by *Merce-Vidal et al* (wherein the substituent is located at position 3) and recited by the instant claims. Nevertheless,

Filla et al indicates that substitution of the indole core at position 1 does not disrupt the compound's activity as a 5-HT6 modulator. The fact that the compounds taught by *Filla et al* do not contain the **exact** substituent at position 1 as is taught in the instant claims would not dissuade the person of ordinary skill in the art from making the compounds since the skilled artisan would seek to ring-walk to the substituent taught by *Merce-Vidal et al* to a position (such as position 1 as taught by *Filla et al*) capable of supporting a similar substituent and maintaining activity as a 5-HT_6 modulator. As such, as discussed above, the skilled artisan - who would ordinarily contemplate making isomers of the compound taught by *Merce-Vidal et al* to try to obtain compounds with improved properties - would consider ring-walking the moiety to position 1 of the indole core with the reasonable expectation that compounds possessing such modification would still function as 5-HT_6 modulators and possibly possess improved properties.

8. Accordingly, for all of the foregoing reasons, Applicants' arguments are not found persuasive. The rejection of claims 18-19, 46-47, 74-75, 84-85 and 92-93 in the previous Action and which are not specifically traversed beyond the traversals discussed above is maintained.

9. The rejection of claims 9 and 86-90 based on N-[3-(2-dimethylaminoethyl)-1H-indole-5-yl]-naphthalene-1-sulfonamide (Page 5, Line 3, Example 8) having the following structure:



in the previous Action is also maintained for the same reasons as discussed above.

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614